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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CLOW, LORI A	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 09/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,773	NOEL ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 18-28* is/are pending in the application.

4a) Of the above claim(s) *19-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 24 May 2004, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-12 and 18-28 are currently pending. Claims 13-17 have been cancelled. Claims 19-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1 October 2003.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Pin1 WW domain, does not reasonably provide enablement for all WW domains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of

experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to determine the ability of a potential binding agent to compete with a known WW domain substrate for binding to a WW domain, wherein the potential binding agent is modeled on a computer to fit spatially into a WW domain interaction site. For the reasons discussed below, this constitutes undue experimentation.

b) The specification provides examples for the Group IV WW domain of Pin1 that specifically interacts with phosphorylated serine and threonine residues that are amino-terminal to proline. Functional and structural basis for WW domain binding to phosphorylated protein substrates based upon the energetic and structural analysis on Pin1-phosphopeptide complex are provided (page 5, lines 8-15). In addition the atomic coordinates of Pin1 are provided in Table 1 (page 14-page 39). However, no examples are provided for other WW domains, such as Group I domains, exemplified by YAP65 which recognize PpxY motifs; Group II WW domains, like FE65, which bind the PPLP motif, Group III WW domains, which interact with PGM motifs, or Group V WW domains, which recognize PGR motifs. As such, one of skill in the art would not know how to use the claimed invention to determine the ability of a potential binding agent to compete with any known WW domain substrate without the knowledge of the functional and structural information for each and every WW binding domain.

c) The specification provides working examples of protein purification and crystallography of a Pin1-peptide complex, binding analysis of a Pin1 domain, architecture of Pin1 bound to CTD, and affinity analysis of Pin1 for CTD mutants. However, no working examples are present for the other four known groups of WW domains (page 51-55).

d) The invention is drawn to methods for determining the ability of a potential binding agent to compete with ANY known WW domain substrate for binding ANY WW domain.

e) It would have been well known in the art that binding domains vary greatly, as reviewed by Macias et al (FEBS Letters (2002) Vol. 513, pages 30-37):

WW domains are small protein modules composed of approximately 40 amino acids. These domains fold as a stable, triple stranded β-sheet and recognize proline-containing ligands. WW domains are found in many different signaling and structural proteins, often localized in the cytoplasm as well as the cell nucleus. Based upon analysis of seven structures of WW domains, we discuss their **diverse** binding preferences and sequence conservation patterns" Such research, however, is lacking in the current specification (page 30, abstract).

Further:

Group I binds polypeptides with the minimal core consensus PpxY, whereas the other binds ligands with the PPLP motif usually embedded in a long stretch of prolines (Group II). Group III selects poly-P motifs flanked by R or K, whereas Group IV bind to short sequences with phospho-S or phospho-T followed by P, in a phosphorylation dependent manner (page 30, column 2).

As such, one of skill in the art would not know how to use the claimed invention to determine the ability of a potential binding agent to compete with any known WW domain substrate without the knowledge of the functional and structural information for each and every WW binding domain.

f) The skill of those in the art of molecular biology is high.

g) The prior art indicates that WW domains have diverse binding preferences and sequence conservation patterns.

h) The claims are broad because they are drawn to determining any known WW domain binding agent.

The skilled practitioner would first turn to the instant specification for guidance to practice said methods. However, the instant specification does not provide specific guidance to practice these embodiments for each and every known WW domain. The specification discloses only the Pin1 domain. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows that WW domains have diverse binding preferences and sequence conservation patterns. Finally, said practitioner would turn to trial and error experimentation to determine each and every WW domain, crystal structure, and function. Such represents undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8, 9, 11, 12 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raganathan et al. (Cell (1997) Vol.89, pages 875-886; PTO 1449 Reference A24) in view of Lu et al. (US 6,495,376), in further view of Klebe (Journal of Molecular Medicine (2000) Vol. 78, pages 269-281).

The present claims are directed to a method of identifying a WW domain binding agent comprising defining an interaction site based on atomic coordinates obtained from a WW domain crystallized in co-complex with a known WW domain binding agent, substrate, or inhibitor; modeling a potential binding agent that fits the interaction site; contacting the potential binding agent with the WW domain; and determining the ability of the potential binding agent to compete with said WW domain substrate for binding to the WW domain.

Raganathan et al. do disclose both structural and functional analyses of Pin1 (instant claim 2), which is a WW domain containing protein (see abstract). They describe in depth the overall architecture and domain topology of Pin1, which consists of two structural domains organized around a hydrophobic cavity (page 876, column 2-page 877, column 1), the surface

structure properties (page 877, column 2-page 878), the substrate specificity (page 880, column 1-2), and the reaction mechanism (page 880, bottom column 2-page 883, column 2). A crystal structure of Pin1 complexed with a dipeptide is disclosed, as in step (a) of claim 1. Further, computer generated (MOLSCRIPT, Raster3D and RIBBONS software) ribbon models of Pin1 detailing the PPIase domain and the interdomian cavity (see Figure 1, A and B) are disclosed (claims 9 and 17-18). Raganathan et al. do not disclose contacting binding agents and determining the ability of the agent to bind.

However, Lu et al. teach methods and compositions of WW-domains as phosphoserine and phosphothreonine binding modules. The invention relates to methods of modulating protein-protein interactions comprising modulating the binding of WW-domain polypeptides (instant claim 6). The invention also describe molecules which mimic a WW-domain (as required by instant claim 8) (column 2, lines 8-12). The invention further includes a method for modulating the activity of a ligand or ligand-mimic for a WW-domain, or a WW-domain containing polypeptide, wherein the modulation is inhibition or enhancement (column 2, lines 38-45) as in claims 4-5. Furthermore, test substances can act as antagonists or agonists (instant claim 3) (column 3, lines 39-40;column 11, lines 9-17). Furthermore, a WW domain binding agent, NIMA, is disclosed (column 8, lines 27-32) as recited in claim 12. Test substances are added to the WW-domain polypeptide either before or following the addition of the ligand under conditions suitable for maintaining WW-domain and ligand in a conformation appropriate for formation of a combination (column 10, lines 61-65). X-ray and NMR structural analysis are used to identify the salient features of the WW-domain (column 18, lines 23-31). In order to determine the structural basis for binding specificity, mutagenesis, and molecular modeling were

performed on the Pin1 crystal structure (see Example 6 beginning column 24). Polypeptides of Lu et al. can be made de novo, as required by instant claim 11 (see, for example, column 9, lines 44-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the WW domain structural and functional information provided by Raganathan et al. to contact a WW domain with its substrate or to contact the WW domain with a potential binding agent, whether it be an agonist, antagonist, inhibitory agent etc., as is done by Lu et al. The motivation to do so is provided by Raganathan et al. at page 884, which states:

"[...] Pin1 is found exclusively in a macromolecular complex in the nucleus (Lu et al. 1996) and thus might make high-affininty interactions with its **targets** possibly mediated through covalent interaction with Cys-113. [...] The study of the cell cycle phenotype of the Cys-113 mutants should clarify the biological role of this residue in mediating **target** interaction. Structural studies of Pin1 complexes with native substrates and systematic mutagenesis of Pin1 residues implicated in catalysis and substrate recognition should help resolve the mechanism of Pin1-dependent cell cycle regulation".

Neither Raganathan et al. not Lu et al. specifically teach the modeling of a potential binding agent using a computer. However, Klebe et al. disclose that "if the three-dimensional structure of a protein is known, this information can be directly exploited for the retrieval and design of new ligands. Structure-based ligand design is an iterative approach. First of all, it requires the crystal structure or a model derived from the crystal structure of a closely related homolog of the target protein, preferentially complexed with a ligand". He goes on to state that "computational methods supplemented by molecular graphics are applied to assist this step of

hypothesis generation. The features of the protein binding pocket can be translated into queries used for virtual computer screening of large compound libraries or to design novel ligands de novo" (page 269, columns 1-2). Therefore, it would have been obvious to use the crystallographic structural and functional information and binding information available in Raganathan et al. and Lu et al. to determine a binding agent of a WW domain, using the computational methods disclosed by Klebe. The motivation is provided by Klebe, who clearly indicates that structure-based design is a universal tool for understanding the principals of protein-ligand complexes and drug design.

Response to Applicant's Arguments

Applicant argues that "Raganathan et al. do not disclose contacting binding agents and determining the ability of the agent to bind". However, it is noted that this is a proper 35 USC 103 rejection in which the Examiner relies upon a combination of references to teach the claimed invention. It is acknowledged that Raganathan et al. do not teach contacting binding agents, however Lu et al. do teach the binding interaction between a WW-domain and ligand. Lu et al. teach "a method of identifying a substance that modulates the interaction of a WW-domain containing polypeptide and a ligand, wherein the ligand is a phosphoserine or a phosphothreonine ligand, comprising contacting the WW-domain containing polypeptide with one, or more, test substances; maintaining the test substance and the WW-domain containing polypeptide under suitable conditions for interaction; and determining the interaction between the test substance and the WW-domain containing polypeptide, wherein the interaction indicates that the test substance modulates the interaction between the WW-domain containing

polypeptide and the ligand. In one embodiment the interaction between the WW-domain and the ligand that is modulated by the test substance is binding interaction. In another it is enzymatic activity. The binding interaction or enzymatic activity between the WW-domain and ligand can be increased or decreased in the presence of the test substance. Thus the test substance can be an antagonist or agonist of the interaction between the WW-domain and the ligand (column 3, lines 19-40)".

Applicant further argues that "Lu et al. is unable to overcome the deficiencies of Raganathan et al. because Lu et al. do not teach computer modeling". This argument is now moot in view of the new grounds of rejection set forth above.

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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MARJORIE MORAN
PATENT EXAMINER

September 10, 2004
Lori A. Clow, Ph.D.
Art Unit 1631